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Voltage and Pace-Capture Mapping of Linear Ablation Lesions Overestimates Chronic Ablation Gap Size

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ABSTRACT

Aims

Conducting gaps in lesion sets are a major reason for failure of ablation procedures. Voltage mapping and pace-capture have been proposed for intraprocedural identification of gaps. We aimed to compare gap size measured acutely and chronically post-ablation to macroscopic gap size in a porcine model

Methods

Intercaval linear ablation was performed in 8 Göttingen minipigs with a deliberate gap of ~5mm left in the ablation line. Gap size was measured by interpolating ablation contact force values between ablation tags and thresholding at a low force cut off of 5g. Bipolar voltage mapping and pace-capture mapping along the length of the line were performed immediately, and at 2 months, post-ablation. Animals were euthanized and gap sizes were measured macroscopically.

Results

Voltage thresholds to define scar were determined by ROC analysis as <0.56mV (acutely) and <0.62mV (chronically). Taking the macroscopic gap size as gold standard, error in gap measurements were determined for voltage, pace-capture and ablation contact force maps. All modalities overestimated chronic gap size, by 1.4±2.0mm (ablation contact force map), 5.1±3.4mm (pace-capture) and 9.5±3.8mm (voltage mapping). Error on ablation contact force map gap measurements were significantly less than for voltage mapping (P=0.003, Tukey's multiple comparisons test). Chronically, voltage mapping and pace-capture mapping overestimated macroscopic gap size, by 11.9±3.7 and 9.8±3.5mm, respectively.

Conclusions

Bipolar voltage and pace-capture mapping overestimate the size of chronic gap formation in linear ablation lesions. The most accurate estimation of chronic gap size was achieved by analysis of catheter-myocardium contact force during ablation.

KEY WORDS

Ablation gaps, voltage mapping, pace-capture mapping

CONDENSED ABSTRACT

Gaps in ablation sets are a major reason for procedural failure. We compared gap size using pace capture, voltage and contact force maps to chronic macroscopic gap size in a porcine model. All modalities over estimated gap size. Error on contact force measurements were significantly less than for voltage mapping.

WHAT'S NEW?

- This is the first comparison of the accuracy of intra-procedural methods for identifying ablation lesion gaps at determining eventual gap size.
- Voltage, pace-capture and contact force maps overestimated chronic gap size.
- Contact force maps were most accurate in predicting chronic gap size.
- Conduction velocity within the gap correlated with gap size measured macroscopically and on contact force maps.

INTRODUCTION

Radiofrequency ablation forms the cornerstone of invasive management of atrial arrhythmias including atrial fibrillation (AF). Successful ablation involves delivery of radiofrequency (RF) energy to critical areas of atrial myocardium resulting in lesions incapable of electrical conduction. Arrhythmia recurrence post ablation is often attributed to electrically conducting gaps in ablation lesion sets representing failure of formation of durable, transmural and contiguous lesions (1). Indeed, success rates for AF ablation remain modest (2) with recurrent AF associated with reconnection of the pulmonary veins to the body of the left atrium (3). Failure to achieve bidirectional conduction block across ablation lesions increases the risk of arrhythmia recurrence therefore accurate intra-procedural identification of ablation gaps is likely to be essential to achieving long term freedom from arrhythmia (4).

Conducting gaps may remain undetected at the index procedure with pulmonary veins appearing electrically silent due to overlapping local oedema resulting in transitory conduction block (5). Indeed, increased T2 signal on cardiac MRI, an index of interstitial oedema, has been demonstrated within the pulmonary vein encirclement in patients with arrhythmia recurrence compared to those without arrhythmia recurrence (6). Over time, conduction through undetected gaps may resume and potentially result in arrhythmia recurrence (7). Additional intra-procedural techniques for assessing ablation lesion integrity have therefore been proposed. Pace-capture mapping was described by Steven *et al* with loss of local capture correlating with entrance block in 95% of vein pairs (8), with the inclusion of inexcitability along the circumferential ablation line as a procedural endpoint resulting in improved clinical outcomes at 12 months (9). Similarly, analysis of local electrograms at candidate ablation sites may be a useful end-point for assessment of lesion formation during pulmonary vein isolation with higher voltages identifying sites of electrical connection (10).

While the above methods show promise for identification of conducting gaps at the time of ablation, their ability to adequately predict eventual gap size after chronic remodelling of the ablation scar is not known. In this study, we therefore compared gap size measured using pace-capture mapping and voltage mapping to eventual chronic macroscopic gap size in a porcine atrial ablation model. In addition, contact force maps during ablation were created by analysis of ablation tags. Gap sizes determined on these ablation contact force maps using a lower contact force threshold of 5g (11) were also compared to eventual chronic macroscopic gap sizes.

METHODS

Animal model and protocol

The animal protocol complied fully with Danish law governing animal experiments. 8 Göttingen minipigs (41.2±7.2kg) were pre-sedated with intramuscular azaperone (4mg/kg) and midazolam (0.5mg/kg) before general anaesthesia was induced with intravenous ketamine (5mg/kg) and midazolam (0.5mg/kg). All animals were intubated and mechanically ventilated and anaesthesia was maintained with a continuous intravenous infusion of propofol (3mg/kg/hr) and fentanyl (15ug/kg/hr). All animals underwent electroanatomic mapping (EAM) and ablation as described below. After ablation, animals were recovered and returned to the farm for a two-month recovery period. Minipigs were used to ensure minimal growth during this time period. After 2 months, animals were anaesthetised according to the same protocol and underwent repeat EAM. Subsequently animals were euthanized, a midline sternotomy was made and the hearts were removed and perfusion fixed for subsequent analysis.

Electroanatomic mapping and ablation

Two 8Fr right femoral venous sheaths were placed before intravenous injection of 100IU/kg of heparin. A 6Fr decapolar reference catheter was placed in the coronary sinus (CS) under fluoroscopic guidance. An 8Fr ablation catheter (Thermocool, SmartTouch, D curve; Biosense Webster) was advanced to the

right atrium (RA). A right atrial anatomic map was created using the ablation catheter and the Carto 3 electroanatomic mapping system (Biosense Webster). Intercaval linear ablation was performed along the posterior wall of the RA. This region was chosen as it is easily accessible from the femoral vein, is similar in morphology to the human atrium and is easily accessed for subsequent dissection. Before commencing ablation, smooth catheter movement along the proposed line was confirmed. Ablation was performed via the ablation catheter (3.5mm irrigated tip at 17mls/min) at a temperature of 42°C and a power of 30W with sufficient contact force to maintain catheter stability (11). Ablation was performed as a continuous drag with the catheter moved every 30 seconds. A deliberate ~5mm gap was left in the centre of the intercaval ablation line created in each animal. High density voltage mapping was performed with the ablation catheter under CS pacing.

Pace-capture mapping

Pace-capture mapping was performed using bipolar pacing along the length of the intercaval ablation line, with the output set to twice the capture threshold of healthy myocardium (3mA). Adequate contact was confirmed with contact force sensing (mean contact force during pacing of 12g) and capture was defined as consistent capture of the entire chamber (RA) in response to pacing, (Medtronic 5375; 3mA output; 2.0ms pulse width). Sites of pace-capture along the line were marked with Carto tags superimposed onto the voltage map. Bipolar voltage was measured at each attempted pace-capture site and used to perform ROC analysis to define voltage thresholds used in subsequent analysis.

Gap Measurement

Voltage. Gap size on voltage maps was measured using the distance measurement tool on the Carto platform and defined as the largest area of contiguous voltage above the low voltage threshold.

Pace-Capture. Gap size on pace capture maps was determined by measuring the longest length of contiguous pace-capture points within the linear ablation line using the Carto measurement tool. Ablation

Contact Force. Contact force maps during ablation were created by interpolating force data from Carto ablation tags to a maximum of 5mm from each ablation point and thresholding the resulting map at a low force cut-off of 5g. Gap size was determined by measuring the largest contiguous length of force below the threshold value.

Gap Conduction Velocity

To determine the average conduction velocity (CV) within the ablation gap, a region of interest was drawn between ends of the ablation line, and used to extract the interpolated activation times, t, from the Carto local activation time map (Figure 1). Average CV for the gap region, $\bar{v}$, was then calculated as:

$$\bar{v} = \frac{1}{n}\sum_{i=1}^{n}\frac{1}{\|\nabla t_i\|}$$

Where n is the number of elements in the gap region and i is the element index.

Macroscopic analysis

After removal, hearts were suspended in cold normal saline. The aorta and main pulmonary artery were cannulated and the SVC, IVC and pulmonary veins cross-clamped. Retrograde perfusion fixation of the heart was performed using 1L of Karnovsky's fixative (Solmedia Ltd., Shrewsbury, United Kingdom) per heart. The ablation line and surrounding tissue were removed en bloc and mounted in plastic frames. Gap length in the cranial-caudal axis was measured manually on the macroscopic specimens using a ruler.

Statistical Analysis

Data analysis was performed using GraphPad Prism version 6.0c (GraphPad Software, San Diego, California). Continuous variables are presented as mean±SD. Groups were compared using the one-way analysis of variance (ANOVA) with Tukey's multiple comparisons test used to identify differences between groups. A significance level of $P<0.05$ was considered statistically significant.

RESULTS

Procedural and ablation parameters

All eight animals survived the protocol and no animals were excluded from analysis. There were no procedural complications. Intercaval linear ablation with a deliberate gap was achieved in all animals. Mean contact force during ablation was 16g. The dataset collected for each animal consisted of 1) acute post-ablation and chronic bipolar voltage/activation maps 2) acute post-ablation and chronic pace-capture maps 3) ablation contact force maps and 4) chronic macroscopic gap length. An example of a single complete data set is given in Figure 2. A total of 16 electroanatomic maps were included in the analysis with an average of 1380±189 points per map, equivalent to a point density of 9.7±2.8 points/cm^2 (12).

Voltage mapping of non-excitable tissue

Mean bipolar voltage was significantly higher at sites of pace-capture compared to sites of non-pace-capture for both acute (1.64±1.44mV vs. 0.42±0.55mV, P<0.0001, Figure 3A) and chronic (1.67±1.26 vs. 0.48±0.51mV, P<0.0001, Figure 3C) time points. Voltage thresholds to define non-excitable tissue were determined by ROC analysis at acute and chronic time points. Acutely, a bipolar voltage cut off <0.56mV demonstrated a sensitivity of 74% and a specificity of 81% to identify inexcitable tissue assessed by pace-capture mapping (Figure 3B). Chronically, a bipolar voltage cut off <0.62mV was required to achieve similar sensitivity (78%) and specificity (80%). Voltage thresholds of <0.56mV (acute maps) and <0.62mV (chronic maps) were therefore used in the remainder of the study for analysis of voltage maps.

Voltage-, pace-capture- and ablation force-based estimation of gap size

A macroscopic photograph of the intercaval chronic ablation line is shown in Figure 2A. The mean macroscopic ablation gap length was 5.3±1.5mm. Taking macroscopic gap size as the gold standard, errors in gap measurements were calculated for pace capture maps, voltage maps and ablation contact force maps (Figure 4). Immediately post-ablation, both voltage and pace-capture maps over-estimated the eventual

chronic macroscopic gap size, by 9.5±3.8mm and 5.1±3.4mm, respectively. Compared to gap size estimated by acute voltage mapping, ablation contact force maps gave a significantly closer estimate of eventual chronic gap size, overestimating gap size by 1.4±2.0mm (P=0.003, Tukey's multiple comparisons test). Chronically, voltage mapping and pace-capture mapping also both overestimated macroscopic gap size, by 11.9±3.7 and 9.8±3.5mm, respectively. Similar to the acute time point, the error in gap size estimation by ablation contact force mapping was significantly less than that for both voltage mapping and pace-capture mapping (P<0.001 and P=0.002, respectively, Tukey's multiple comparisons test).

Gap region conduction velocity

To determine the relationship between gap size measured by macroscopy, voltage, pace-capture or ablation force maps and intra-gap conduction velocity, regions of the local activation time maps corresponding to the ablation gap were extracted from the acute post-ablation activation maps and mean conduction velocities in these regions were determined. Intra-gap conduction velocity was positively and significantly correlated with gap size determined by both macroscopy and ablation contact force maps (Figure 5). Consistent with the error in gap size measurement reported above for voltage and pace-capture mapping, there was no correlation between voltage or pace-capture gap size and intra-gap conduction velocity at either acute or chronic time points. Correlation co-efficient values and significance values for these relationships are summarized in Table 1.

DISCUSSION

The main findings of this study are 1) post ablation voltage and pace-capture mapping overestimate chronic gap size in linear ablation lesions; 2) gap size determined by analysis of contact force data most accurately estimates chronic gap size; and 3) intra-gap conduction velocity is positively correlated with both macroscopic and ablation force map-defined gap size.

It is well-recognised that acute isolation of the pulmonary veins can be achieved in the absence of irreversible tissue damage. Lesion sets can demonstrate entrance block, an accepted procedural endpoint, even in the presence of obvious visual gaps (5). Local electrophysiological changes around ablation sites including reduction in action potential duration and conduction velocity have been reported in a rabbit model (13) and cardiac MRI studies have demonstrated resolution over time of acute oedema initially seen post ablation (6). As such it is not surprising that chronic lesion formation may be insufficient to ensure complete pulmonary vein isolation. Adjunctive intraprocedural techniques have therefore been described to facilitate assessment of acute lesion sets.

Pace-capture mapping

Pace-capture mapping has been shown to consistently identify gaps in linear ablation sets and to predict the formation of transmural lesions (14–16). We found that pace-capture significantly overestimates macroscopic chronic gap size. Factors such as electrode-tissue contact and catheter orientation should be considered when performing pace-capture evaluation of lesion sets. Kosmidou *et al* demonstrated that loss of bipolar capture was 100% predictive of uniform lesion formation only in the presence of optimal tissue contact (16). Similarly, inadvertent capture of neighbouring endocardium may occur from the proximal ring of the distal electrode of the pacing catheter depending on the angle of orientation (17). In this study, a low pacing output of 3mA was chosen to minimise distant capture.

Voltage Mapping

Change in unipolar and bipolar voltage amplitude at ablation sites can be used to predict lesion formation and transmurality (18). A significant discrepancy was seen in our study between gap size measured acutely and chronically by voltage mapping and eventual macroscopic gap size.

Several factors may influence the interpretation of voltage maps. Thresholding of voltage maps to represent ‘scar’ influences how a region is defined and may result in over or underestimation of scar.

Many centres accept a low voltage threshold value of 0.5mV, and a scar cut off value of 0.05mV as a matter of convention. A number of recent studies have attempted to define voltage thresholds associated with dense scar. We have previously described a mean bipolar voltage of 0.6mV and 0.3mV in acute and chronic ablation scar respectively in swine (19). Squara *et al* described loss of pace capture as a method of reliably identifying post ablation scar (10) and we employed this method in this study to define scar voltage thresholds. The values obtained acutely and chronically to predict inexcitable scar (0.56mV and 0.62mV respectively) in this study are higher than previously described and significantly higher than the commonly-employed threshold of <0.05mV (20).

Other factors to consider include activation direction, rate of activation and local conduction velocity which have all been associated with changes in voltage amplitude in atrial and ventricular myocardium (21–23). Mapping resolution, relating directly to mapping catheter electrode size and spacing, may also influence the appearance of voltage maps. Voltage may be influenced by electrode size (24) and multi-electrode mapping catheters (with smaller electrodes and closer inter-electrode spacing) have demonstrated superior resolution with better delineation of low voltage zones when compared to ablation catheters (25,26). Given these findings a possible cause for the overestimation of gap size by voltage mapping in this study may be the large distal electrode (3.5mm) and wider bipolar spacing of the ablation catheter. Considering the superior ability of multi-electrode catheters, with smaller electrodes, to identify areas of preserved voltage within low voltage zones (25), new ultra high-density mapping systems may demonstrate better estimation of true gap size than seen in this study.

Ablation Contact Force

Gap measurements on contact force maps created from ablation tags most closely approximated eventual macroscopic gap size (27,28). The relative accuracy of these maps highlights the importance of creating a contiguous lesion set. Indeed, inter-lesion distance has been shown to be significantly higher in ablation

segments with pulmonary vein reconnection compared to segments without (4). A 'point by point' workflow for pulmonary vein isolation, focusing on avoiding visual gaps, maintaining catheter stability and achieving pre-defined ablation parameters may optimise the creation of contiguous, transmural lesions (29). Although results of prospective trials evaluating this technique are still awaited the present study further emphasises the importance of achieving contiguous ablation tag appearances during ablation.

Clinical Relevance

In current clinical practice, linear ablation is most commonly employed as an adjunct strategy in those with persistent AF or those undergoing redo procedures, for example to achieve posterior LA wall isolation. In this study we used linear ablation as a model of contiguous, point by point atrial ablation and argue that these results are relevant to any contiguous lesion set including pulmonary vein encirclement.

This study directly compares gap size using voltage and pace capture maps to eventual macroscopic measurements. Overestimation of gap size by voltage mapping and pace-capture mapping may result in unnecessary additional ablation which could increase the risk of collateral tissue damage. These findings may also be of relevance when performing post ablation voltage mapping during repeat ablation procedures. Our findings in relation to conduction velocity (Figure 5) are in line with prior work in canine models demonstrating higher rates of block in smaller (<5mm) gaps (30). Small gaps between otherwise contiguous ablation lesions may increase the risk of post ablation clinical atrial tachycardia resulting from a larger excitable gap due to lower conduction velocity within the gap (31). The comparative accuracy of contact force maps in predicting eventual gap size in this study underlines the importance for operators to focus on achieving contiguous, effective ablation during the index procedure.

LIMITATIONS

The results presented in this study describe methods of ablation line gap size estimation in a porcine model. While the porcine right atrium closely resembles the human left atrium in terms of tissue thickness,

we acknowledge the inherent limitation posed by extrapolating findings from animal models to humans. Ablation was performed in this study as a slow drag lesion rather than point by point ablation. Titrated RF delivery using a point by point work flow may represent a more effective method of linear ablation, however to the best of our knowledge there are no comparative studies demonstrating histological differences between continuous and point-by-point ablation. Furthermore, in a previous study using the same ablation model we demonstrated effective lesion formation throughout the ablation line (11). Bipolar pacing may have resulted in a wide area of tissue capture resulting in overestimation of gap size (see above in 'Discussion'). Whether unipolar pacing would have resulted in more accurate estimation of gap size cannot be determined from this data.

CONCLUSION

Voltage and pace-capture mapping along ablation lines may be used as intra-procedural tools to identify gaps in acute lesion sets. Both these techniques over estimate eventual gap size as defined by chronic macroscopic assessment. Contact force maps created from ablation tags demonstrated the greatest accuracy in predicting eventual gap size. Further work is needed to evaluate the integrity of lesion sets created using a point by point work flow focused on contiguous lesions meeting pre-defined ablation parameters.

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APPENDICES

Table 1. Correlations between gap size and conduction velocity.

Gap measurement method	Correlation with intra-gap conduction velocity	
	R^2	P
Macroscopy	0.5954	0.0249 *
Force map (acute)	0.5615	0.0323 *
Pace-capture (acute)	0.2852	0.1728
Voltage (acute)	0.0269	0.6982
Pace-capture (chronic)	0.0504	0.5928
Voltage (chronic)	0.0897	0.4712

* indicates statistical significance ($P<0.05$).

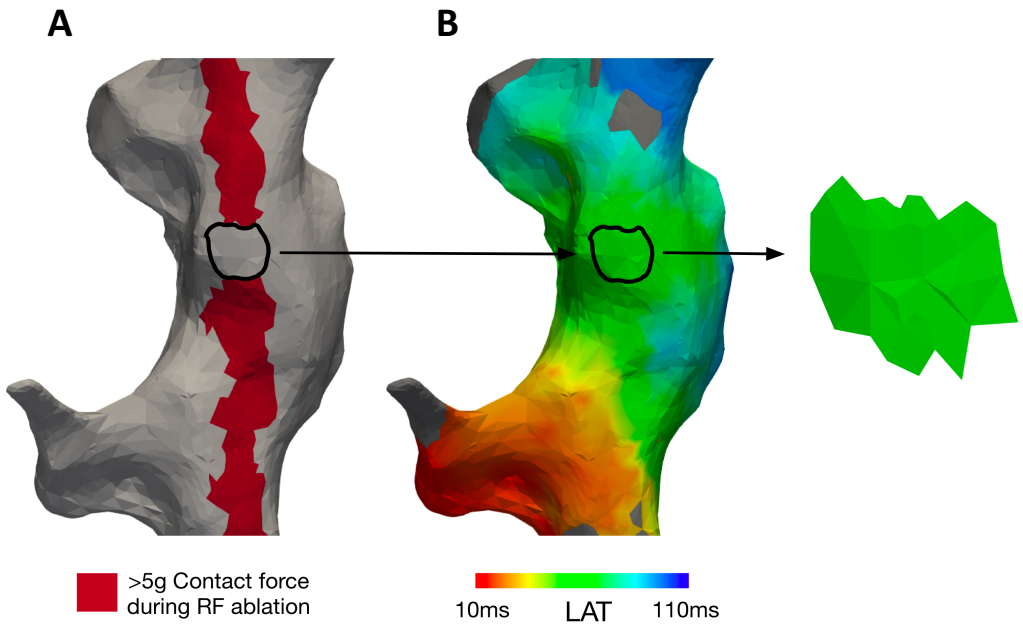

Figure 1. Gap Region Definition.

A. Map demonstrating the linear ablation lesion. Red indicates the area where a contact force of > 5g was achieved. **B.** Activation map from which a region of interest corresponding to the gap in the ablation line was extracted to allow calculation of conduction velocity within the gap.

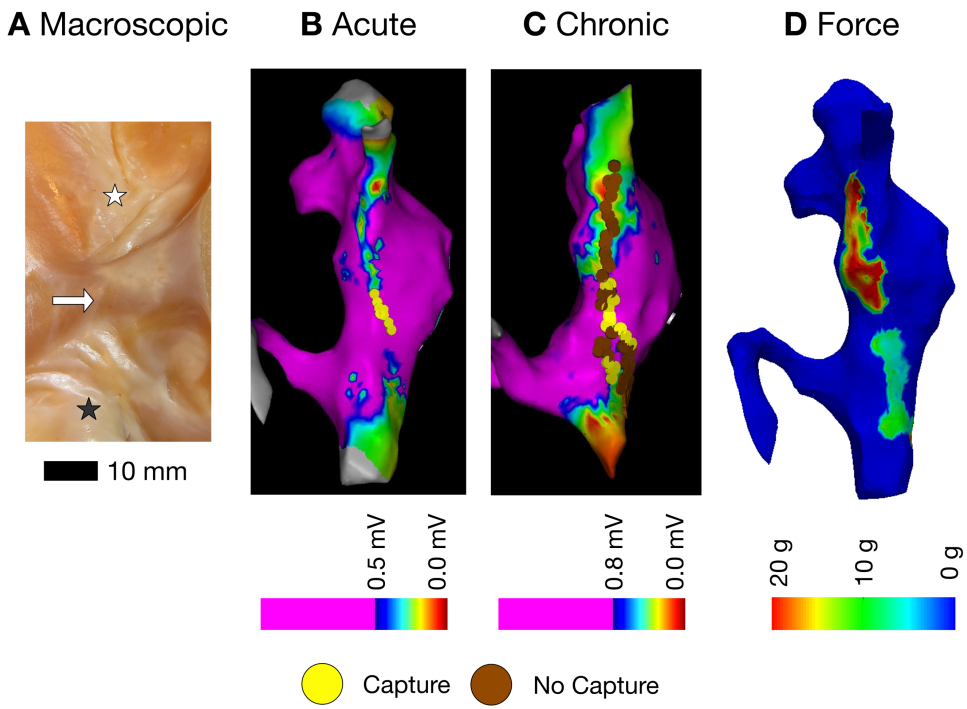

Figure 2. Study Data.

A. Macroscopic gap assessment. Gap in ablation line (white and black stars) is indicated by a white arrow. **B.** Acute post ablation (<30mins) voltage and pace-capture map. Lower voltage threshold set at 0.56mV. Sites of pace-capture indicated by yellow tags. **C.** Chronic post ablation (2 months) voltage and pace-capture map. Lower voltage threshold set at 0.62mV. Sites of pace-capture indicated by yellow tags, sites of no pace-capture indicated by brown tags. **D.** Ablation tag/contact force maps. Contact force data from the Carto 3 system was interpolated to within 5mm of each ablation tag and thresholded at a force of 5g.

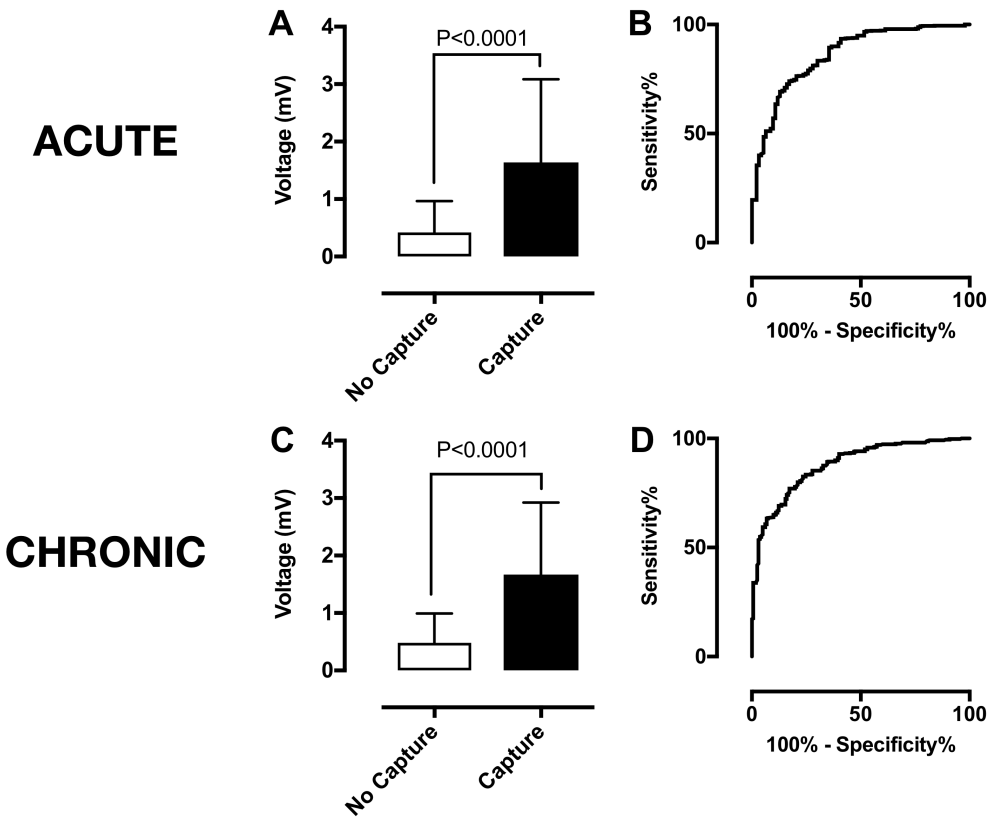

Figure 3. Bipolar Voltage Characteristics at excitable and non-excitable sites.

A. Mean bipolar voltages at sites of acute pace-capture are higher than at sites of non-capture. **B**. ROC analysis for acute bipolar voltage/pace-capture. **C.** Mean bipolar voltage at sites of chronic pace-capture are higher than at sites of non-capture. **D**. ROC analysis of chronic bipolar voltage/pace-capture.

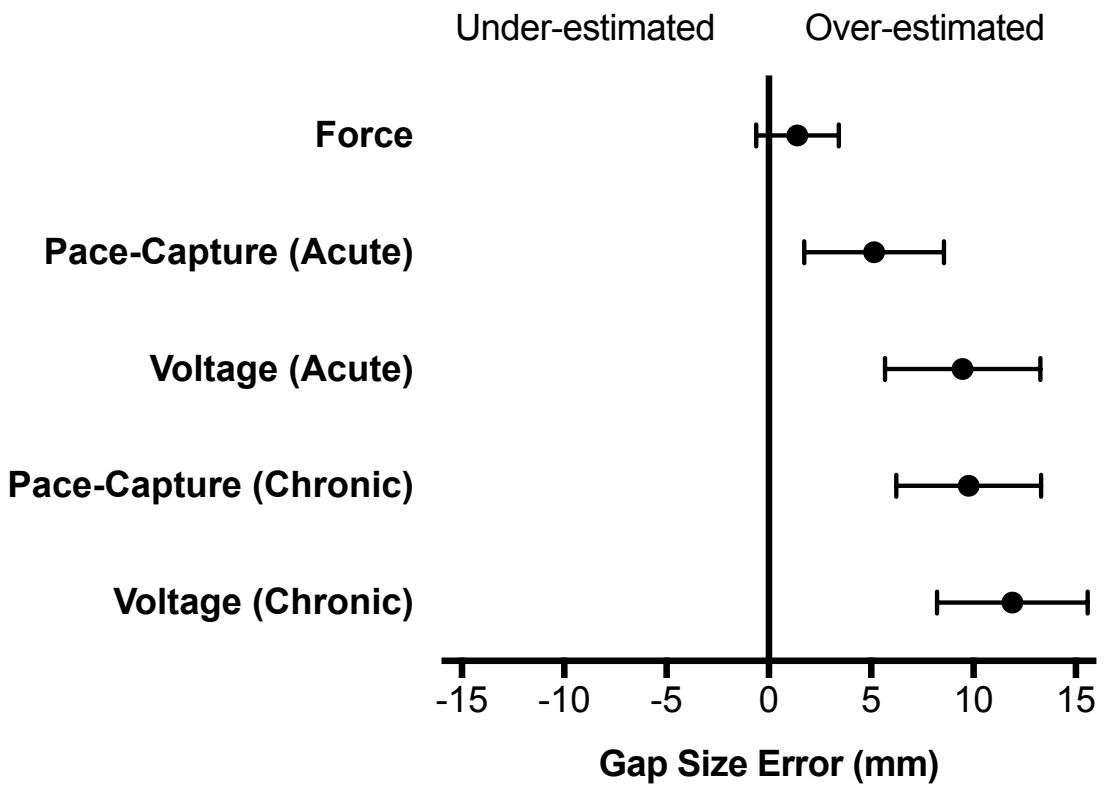

Figure 4. Representative Figure. Gap Size Errors.

Intraprocedural gap measurement errors. Gap size as determined by force maps and pace-capture and voltage maps at acute and chronic time points were compared to eventual chronic macroscopic gap size.

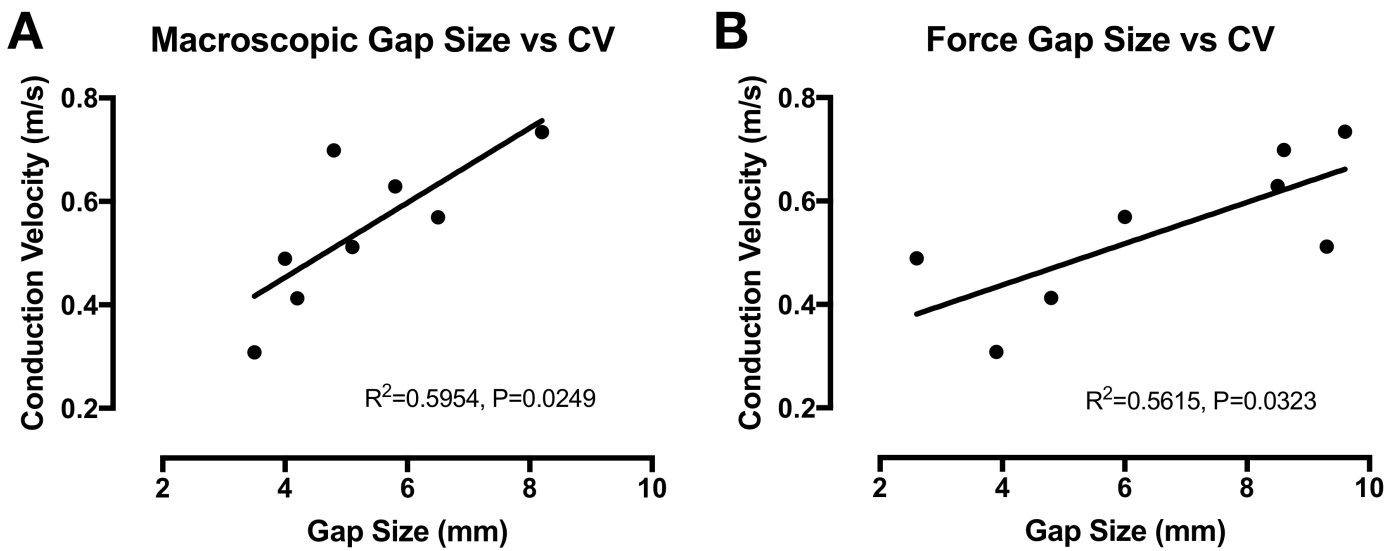

Figure 5. Relationship Between Gap Size and Conduction Velocity.

A. Conduction velocity was positively correlated with gap size determined by macroscopic assessment. **B.** Conduction velocity was positively correlated with gap size determined by analysis of ablation contact force maps at a low force cut off threshold of >5g.